REMARKS

Claims 79-83, 85-116, and 122-131 are pending in this application. Claims 79, 80, 83, 85-87, 89, 92-95, 97-99, 101-107 and 111-116 are allowed. Claims 1-78, 84, and 117-121 have been canceled without prejudice. Applicants reserve the right to file one or more divisional, continuation, or continuation-in-part applications directed to any withdrawn or canceled subject matter.

Claims 88, 90, 91, 95, 96, 100, 130 and 131 have been amended herein. Claims 88 and 96 have been amended to specify that the claimed variants include "one or two amino acid substitutions" having "analogous physicochemical properties" to those of the replaced amino acids. Claims 130 and 131 have been amended to indicate that the single amino acid substitution has "analogous physicochemical properties to that of the replaced amino acid." Support for the amendments to claims 88, 96, 130 and 131 can be found for example, at page 11, last paragraph and in Table 1 on page 12. Claim 90 was amended to indicate that the recognition molecule of claim 87 comprises "SEQ ID NO:32 and SEQ ID NO:34." Support for this amendment can be found, for example, on page 23, penultimate paragraph and on page 92 in the sequence listing. Claims 91 and 100 have been amended to more clearly identify the sequences comprising the recognition molecules according to claims 87 and 95, respectively. Support for the amendments to claims 91 and 100 can be found, for example, on page 27, first paragraph, page 32, first full paragraph, page 64, first full paragraph, and in the sequence listing on pages 96-99. Claim 95 was amended to more clearly indicate which amino acid sequences the recombinant recognition molecule comprises.

No new matter has been added by the amendments.

I. Examiner Interview on September 2, 2010

Applicants wish to thank Examiner Gussow for taking the time to meet with the undersigned attorney and Patrick Fogle, attorney for Applicants, on September 2, 2010. Applicant's amendments and remarks herein reflect the agreements reached during the interview related to the current written description rejection, for which the office relies on references Rudikoff et al, Casset et al, De Pascalis et al, and Vajdos et al.

II. The Objection to Claims 81, 82, 90, 91, 100 and 108-110 is Rendered Moot

A. Objection to Claims 90, 81, 82, and 108-110

Claim 90 was objected to because it allegedly failed to "further limit claim 87 because the CDR sequence of SEQ ID NO. 11 is not a CDR in SEQ ID NO.33 or 35." Office Action, page 3, paragraph a. Claims 81, 82, and 108-110 were included in the objection because they depend from claim 90.

Applicant have amended claim 90 herein to indicate that the recognition molecule of claim 87 comprises "SEQ ID NO:32 and SEQ ID NO:34." Accordingly, the CDR sequence of SEQ ID NO.11, as well as the CDR sequences of SEQ ID NOs. 1, 3, 5, 7 and 9, as indicated in claim 87, is a CDR sequence included in SEQ ID Nos. 32 and 34. Thus, claim 90, as amended herein, further limits claim 87. Consequently, this objection is rendered moot and withdrawal thereof is respectfully requested.

B. Objection to Claim 91

Claim 91 was objected to because it allegedly failed to "further limit claim 87 because the sequences of SEQ ID NOs. 60, 62, 64, 66 and 68 do not include all of the CDRs of claim 87." Office Action, page 3, paragraph b. The Action further indicates that SEQ ID NOs. 60, 62, 64 and 66 comprise SEQ ID NOs. 1, 3 and 5 and that SEQ ID NO. 68 comprises SEQ ID NOs. 7, 9, and 11.

Initially, Applicants note that SEQ ID NOs. 36-47, and 62, 64 and 66 comprise SEQ ID NOs. 1, 3, and 5 and that SEQ ID NOs. 60 and 68 comprise SEQ ID NOs. 7, 9 and 11. Accordingly, Applicants have amended claim 91 to indicate that the recognition molecule of claim 87 comprises: "(i) at least one sequence set forth in SEQ ID NOs 36 to 47, (ii) SEQ ID NO: 60 and SEQ ID NO: 62, (iii) SEQ ID NO: 64 and SEQ ID NO: 66, or (iv) SEQ ID NO:66 and SEQ ID NO: 68." As amended, each of the recognition molecules in claim 91 now include CDRs of SEQ ID NOs. 1, 3, 5, 7, 9 and 11 and thus further limits claim 87. Consequently, this objection is rendered moot and withdrawal thereof is respectfully requested.

C. Objection to Claim 100

Claim 100 was objected to because it allegedly failed to "further limit claim 95 because the sequence of SEQ ID NOs. 61, 63, 65, 67 and 69 do not include all of the CDRs of claim 95." Office Action, page 3, paragraph c. The Action further indicates that "[t]hese sequences only include SEQ ID NOs. 2, 4, and 6, (SEQ ID NOs. 61, 63, 65, and 67) or 8, 10, and 12 (SEQ ID No. 69)." *Id.*

In response, Applicants have amended claim 100 to indicate that the recognition molecule of claim 95 comprises: "(i) at least one sequence set forth in SEQ ID NOs 48 to 59, (ii) SEQ ID NO:61 and SEQ ID NO:63, (iii) SEQ ID NO:65 and SEQ ID NO:69, or (iv) SEQ ID NO:67 and SEQ ID NO:69." As amended herein, each of the recognition molecules in claim 100 now include CDRs of SEQ ID NOs. 2, 4, 6, 8, 10 and 12. Consequently, this objection is rendered moot and withdrawal thereof is respectfully requested.

III. The Objection of Claim 117 is Rendered Moot

Claim 117 was objected to "under 37 CFR 1.75 as being a substantial duplicate of claim 87." Office Action, page 3, paragraph 6. Applicants have cancelled claim 117 herein. Consequently, the objection is rendered moot and withdrawal thereof is respectfully requested.

IV. The Rejection Under 35 U.S.C. § 112, First Paragraph Should be Withdrawn

The rejection of claims 88, 96, 130 and 131 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement was maintained. The Office Actions states that "while Applicant has defined 'equivalent canonical structural variants' in the specification, the definition encompasses amino acid substitutions at any amino acid position in the CDRs." Office Action, page 8, third paragraph. (Emphasis added). Furthermore, the Action acknowledges that although "applicant is not required to describe each and every species of a claimed genus, one must describe a sufficient variety of species to reflect the variation within the genus" and that "written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus." *Id.* Applicants respectfully disagree and traverse as follows.

The written description requirement requires that applicants convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The Federal Circuit has held that possession requires the disclosure of "a representative number of species falling within the scope of the genus or structural features common to the members of the genus so that one of skill in the art can 'visualize or recognize' the members of the genus." *University of California v. Eli Lilly & Co.*, 119 F.3d 1559 (Fed. Cir. 1997). However, "[a]n invention claimed need not be described *ipsis verbis* in the specification in order to satisfy the disclosure requirements." *Ex parte Eggleston* (BPAI 2005) (not precedent).

Additionally, the written description requirement does not demand either examples or an actual reduction to practice. Indeed, a constructive reduction to practice that in a definite way identifies the claimed invention can satisfy the written description requirement. *Ariad Pharmaceuticals v. Eli Lilly* (2008-1248 (Fed. Cir., March 22, 2010) (*en banc*).

During the interview on September 2, 2010, Applicant's representatives discussed with Examiner Gussow a proposal to amend claims 88 and 96 to recite variants in which "one or two amino acids are replaced by an amino acid with analogous physicochemical properties" in order to overcome the outstanding written description rejection. Applicants have amended claims 88, 96, 130 and 131 to incorporate this recitation.

Applicants respectfully assert that the specification provides those of skill in the art at the time the application was filed with the information sufficient to convince them that the Applicants were in possession of the now claimed recombinant recognition molecules.

A. Description in the Specification

The specification provides specific structural guidance as to which amino acid substitutions would provide an analogous property and/or functional group when compared to the amino acid that is replaced. Specifically, the specification provides that "[a]mino acids having analogous physicochemical properties in the meaning of the invention can be summarized into 6 separate groups and are illustrated in Table 1." Specification at p.11, last paragraph.

Moreover, the specification describes exemplary CDR substitutions and canonical structural variants. *See* Exhibit A (attached hereto).

Therefore, the specification provides specific guidance to the skilled artisan to determine a suitable amino acid substitution by amino acid *type* and *position*. (*see* Table 1)

B. The Office's Position

To support the current rejection, the Office relies on Rudikoff, De Pascalis, Casset and Vajdos and refers the Applicants to the discussion related to these references provided in the previous office action mailed November 4, 2009 (hereinafter "the First Office Action"). The Office indicated that the "mutation of a single amino acid residue may dramatically affect antigen binding…and residues other than the CDR residues are essential for the structure of the antigen binding site." *See* Office Action, page 5, first paragraph. (emphasis added).

During the Interview on September 2, 2010 and in a phone message from Examiner Gussow on September 15, 2010, the undersigned were made aware that Office would be exceedingly unlikely to allow claims directed to CDR variants which were not expressly described in the Application. Applicants glean from this position that the Office assumes that single amino acid changes in CDR are ostensibly wildly unpredictable and that the skilled artisan would not believe that individual functional variants could be possessed unless expressly identified.

Applicants concede that the specification does not disclose ALL of the possible functional variants encompassed by the claims. However, that has never been required by the Federal Circuit. What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail. See *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1379-80, at 1384, 231 USPQ at 94; *Capon v. Eshhar*, 418 F.3d 1349, 1357, 76 USPQ2d 1078, 1085 ("The 'written description' requirement must be applied in the context of the particular invention and the state of the knowledge…"). Again, the standard is what the skilled artisan would have thought the applicants "possessed" in view of what was disclosed and the state of the art.

Applicants respectfully assert that the person of skill in the art at the time of filing of the present invention would have known that CDRs are amenable to a substantial number of amino acid substitutions without significant effect on antigen binding. They would have been particularly convinced that this is true with respect to the substitution of functionally analogous amino acids.

During the interview with Examiner Gussow, Applicants emphasized that none of the references relied upon by the Office for the current rejection in fact, teaches that changes in the CDR necessarily (or are even highly likely to) destroy antibody-antigen binding.

Indeed, Applicants pointed out that the references in fact, teach the opposite: That the majority of amino acid substitutions in the CDR are not likely to have an impact on binding.

Applicants respectfully point out that the Office "[a]greed that the references [i.e., Rudikoff, Casset, DePascalis and Vajdos] teach that such substitutions [in the CDRs with amino acids having one or two analogous physiochemical properties] are unlikely to result in a loss of antigen binding." Interview Summary mailed Sept. 3, 2010.

1. Rudikoff et al.

Notwithstanding, the fact that Rudikoff uses the term "may" and not "must," the Office appears to take the scientifically untenable position that any modification of a CDR must (or is at least is highly likely to) dramatically affect antibody-antigen binding.

The Office asserted that Rudikoff states that"[e]ven minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function" and that "Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function." First Office Action, page 6, first paragraph. Although Applicants agree that the Rudikoff reference identifies an incident where a single amino acid substitution altered antigen-binding specificity, Applicants note that Rudikoff emphasizes that this incident where antigen binding is affected by a single amino acid modification is the exception rather than the rule.

While "a single amino acid substitution is capable of completely altering antigen-biding specificity" Rudikoff concluded that "it is clear that all such substitutions need not and probably do not affect antigen binding." Rudikoff, page 1982, paragraph bridging left and right columns. (emphasis added). Rudikoff follows-up with this conclusion by providing examples where, "the heavy chain from the P-Cho-binding myeloma protein M167 differs from that of S107 at 13 positions…and yet has an association constant for hapten only slightly lower than S107" and that "among anti-1,6-galactin-binding myeloma proteins, as many as eight or nine substitutions may occur in hypervariable regions with no significant effect on hapten affinity or specificity." *Id.* (emphasis added).

Accordingly, a person of skill in the art reading Rudikoff would not have felt that modifications in antibody CDRs were likely to significantly affect antibody-antigen binding. As

such, those modifications were within the general knowledge as largely inconsequential and as such, need not be described. *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1379-80, at 1384, 231 USPQ at 94; *Capon v. Eshhar*, 418 F.3d 1349, 1357, 76 USPQ2d 1078, 1085

2. Casset et al.

Casset was cited by the Office for representing the "fact that not just one CDR is essential for antigen binding or maintaining the conformation of the antigen binding site." First Office Action, page 6, last paragraph. Casset teaches the development of a peptide mimetic of an anti-CD4 antibody, which contains antigen contact amino acid residues, defined as active chemical groups for binding activity, that are derived from multiple CDRs. The peptide mimetic was developed using peptide mapping to determine active antigen recognition residues, molecular modeling, and molecular trajectory analysis. *See*, Casset Abstract and page 199, third paragraph.

In particular, Casset used alanine scanning to analyze the amino acid sequences of the variable regions of the ST40 antibody to identify each of the important as well as the less important amino acid residues in the CDRs. *See* Casset, Figure 1. Moreover, of the important residues identified within the CDRs, only a small number of these were actually included in the ST40 mimetic. Importantly, although lower than that of the parent antibody ST40, the mimetic still displayed an affinity for the CD4 antigen.

3. Vajdos et al.

Similar to Casset, Vajdos performed alanine scanning as well as systematic replacement of amino acids with similar physicochemical properties (i.e., homolog scanning) through a shotgun scanning approach to identify amino acid residues of the Fab2C4 CDRs important in for ErbB2-ECD antigen binding. *See* Vajdos, Figure 1, page 417. Vajdos found that "only a subset of the side chains that were intolerant to alanine substitutions were also intolerant to homologous substitutions." *Id.* at Abstract. In particular, Vajdos determined that "[s]ubstitutions for eight of the nine buried light chain residues have little effect on ErbB2-ECD binding" and that "most buried heavy chain residues appear to be involved in scaffolding interactions that are critical for antigen binding." *Id.* at 424, first and second paragraphs.

Vajdos in Figure 2, demonstrates that whereas 12.5% (3/24) of light chain CDR amino acid residues substituted with alanine resulted in an $F_{wt/mut}$ greater than 10 (i.e., indicating that a position contributes significantly to the binding affinity of Fab2C4 for ErbB2-ECD; exactly none

(0/24) of light chain CDR amino acid residues substituted with an homologous amino acid resulted in an $F_{wt/mut}$ great than 10. The figure also shows that similar alanine and homologous amino acid substitutions in the heavy chain CDRs resulted in an $F_{wt/mut}$ greater than 10 in 53% (18/34) and 38% (13/34) of amino acid positions, respectively. Taken together the skilled artisan would have thought that homologous amino acid substitutions either the heavy or light chain CDRs would be exceedingly unlikely to have a significant impact on antigen binding.

As such, Vajdos would also have taught the skilled artisan to believe that minor CDR variation is largely inconsequential with respect to antigen binding – particularly where the substitution is with analogous amino acids. The Federal Circuit does not require that such inconsequential and known variation be expressly disclosed. *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1379-80, at 1384, 231 USPQ at 94; *Capon v. Eshhar*, 418 F.3d 1349, 1357, 76 USPQ2d 1078, 1085

4. De Pascalis et al.

De Pascalis was cited as demonstrating that CDR residues and framework residues were "deemed essential for preserving the structural integrity of the antigen binding site" and thus could not be substituted without affecting antigen binding. First Office Action, page 6, second paragraph. The Office further emphasized that "[a]lthough abbreviated CDR residues were used in the constructs, some residues in all 6 CDRs were used for the constructs." *Id.*

Applicants point out that De Pascalis is not concerned with altering CDRs. Instead, De Pascalis involved typical CDR-grafting in the humanization of an antibody. *See* De Pascalis at Abstract. Specifically, De Pascalis utilized a humanization protocol for mAb COL-1 to identify the CDR residues that are involved in the antigen binding with carcinoembryonic Ag (CEA) and proposed redefining the CDR boundaries. *Id.* at pg. 3080, left-hand column, second paragraph and Figure 2, page 3079.

De Pascalis showed that one or more residues from the donor CDR can be "omitted" when grafting the donor CDR onto a human acceptor framework. De Pascalis showed that not all residues of a CDR are involved in antigen binding. *Id.* at 3083, left-hand column, second paragraph. In fact, De Pascalis in referencing Padlan et al., notes that "[e]xamination of the known structures of Ab-Ag complexes reveals that only one-third of the CDR residues are involved in the interaction with the Ag." *Id.* at 3080, left-hand column, second paragraph.

One of skill in the art would have concluded that applicants were in possession of recognition molecules having one or two analogous amino acid substitutions in the CDRs since in the majority of instances the variants do not significantly affect antigen binding.

The results described above, indicate that the replacement of an amino acid residue in a CDR with a "homologous" amino acid in most cases does not alter the antigen-binding specificity of the antibody. Thus, with respect to the present invention, since the claims as amended require that one or two amino acids in the CDRs are replaced by amino acid residues having "analogous physicochemical properties," the skilled artisan would deem that the claimed variants would not alter the MUC1 binding properties. Again, that which is known, need not be described in the specification. *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1379-80, at 1384, 231 USPQ at 94; *Capon v. Eshhar*, 418 F.3d 1349, 1357, 76 USPQ2d 1078, 1085

In conclusion, Applicants respectfully submit that the specification provides an adequate description of the claimed invention, including the structural elements of sequences, a description of appropriate analogous physicochemical amino acid substitutions, known methods of determining canonical classes and "equivalent canonical structural variants," and assays to assess if a recognition molecule binds to a glycosylated MUC1 tumor epitope. Moreover, the references cited by the Office (i.e., Rudikoff, Casset, Vajdos and De Pascalis) show that in the majority of instances that limited amino acid substitutions in the CDRs with amino acids sharing physicochemical properties are unlikely to have an impact on antigen-antibody binding.

The totality of this information requires a conclusion that the full scope of the present claims was in the possession of the inventors at the time the claimed invention was made. Based on at least the arguments set forth above, Applicants respectfully request that the rejection of the claims under 35 U.S.C. § 112, first paragraph be reconsidered and withdrawn.

V. The Rejection of Claim 117 Under 35 U.S.C. § 101 is Rendered Moot

Claim 117 was rejected under 35 U.S.C. § 101 because "the claimed invention is directed to non-statutory subject matter." Applicants have cancelled claim 117 herein. Consequently, the rejection is rendered moot and withdrawal thereof is respectfully requested.

VI. Conclusion

Applicants believe that claims 79-83, 85-116, and 122-131 are allowable and respectfully request allowance thereof. The Examiner is invited to telephone the undersigned if that would be helpful to resolving any issues.

It is believed no fees are due; however, the commissioner is authorized to charge any fees and credit any overpayments to Deposit Account No. 50-5071 which may be due.

Respectfully submitted,

Date: September 17, 2010

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